ORİJİNAL ARAŞTIRMA ORIGINAL RESEARCH

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The Relationship Between Whole Blood Viscosity and Deep Vein Thrombosis

Tam Kan Viskositesi ile Derin Ven Trombozu Arasındaki İlişki

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ABSTRACT Objective: This study aimed to investigate the potential relationship between whole blood viscosity (WBV) and deep vein thrombosis. **Material and Methods:** In this study, 50 patients who applied to the cardiovascular surgery and cardiology policlinic and were diagnosed with deep vein thrombosis between January 2016 and January 2018 and additionally 44 healthy people were included in the study as a control group. The estimation of WBV was carried out at both high shear rate (HSR) (208/s) and low shear rate (LSR) (0.5/s) by previously validated formulate using hematocrit (HcT) and total protein (TP) in g/L. WBV at HSR (208/s) is: (0.12 × HcT) + 0.17 (TP-2.07) and WBV at LSR (0.5/s) is: (1.89 × HcT) + 3.76 (TP-78.42). The whole blood viscosity of deep vein thrombosis patients and of control group were compared at both HSR and LSR. **Results:** Age and gender distribution of the patients included in the study were similar. Hemoglobin, platelet count, and total protein were substantially higher in the group with deep vein thrombosis (p=0.04, p=0.002, p=0.022, respectively). Likewise, WBV of patients with deep vein thrombosis was substantially higher than the control group, at both low-shear rate and high-shear rate (P=0.023 for LSR and p=0.031 for HSR). A multivariate analysis showed that the whole blood viscosity for both shear rates were independent from the risk factors of deep vein thrombosis (WBV at LSR, OR=5.00; 95% CI, 2.037-12.269; P<0.001 and WBV at HSR, OR=1.068; 95% CI, 1.028-1.110; P=0.001). **Conclusion**: In conclusion, whole blood viscosity is found out to be an important and independent risk factor in patients with deep vein thrombosis.

Keywords: Blood viscosity; venous thrombosis

ÖZET Amaç: Bu çalışmanın amacı, tam kan viskozitesi (TKV) ve derin ven trombozu arasındaki olası ilişkiyi araştırmaktı. **Gereç ve Yöntemler:** Bu çalışmada, Ocak 2016 ile Ocak 2018 arasında kardiyovasküler cerrahi ve kardiyoloji polikliniğine başvuran ve derin ven trombozu tanısı alan 50 hasta ile kontrol grubu olarak 44 sağlıklı kişi çalışmaya dahil edildi. TKV, hematokrit (HcT) ve toplam protein (TP) kullanılarak önceden doğruluğu kanıtlanmış formüller ile hem yüksek sürtünme hızında (YSH) (208/s) hem de düşük sürtünme hızında (DSH) (0.5/s) hesaplandı. YSH'de (208/s) WBV: (0.12 x HcT) + 0.17 (TP-2.07) ve DSH'de (0.5/s) WBV: (1.89 x HcT) + 3.76 (TP - 78.42). Tam kan viskozitesi, hem YSH hem de DSH'de derin ven trombozu hastaları ile kontrol grubu arasında karşılaştırıldı. **Bulgular:** Çalışmaya dahil edilen hastalar benzer yaş ve cinsiyet dağılımına sahipti. Derin ven trombozu olan grupta hemoglobin, trombosit sayısı ve total protein anlamlı olarak yüksek bulundu (sırasıyla p=0.04, p=0.002, p=0.022). Derin ven trombozu olan hastaların tam kan viskoziteleri kontrol grubuna göre hem düşük sürtünme hızında hem de yüksek sürtünme hızında anlamlı derecede yüksek bulundu (DSH için P=0.023 ve YSH için p=0.031). Çok değişkenli analizde, her iki sürtünme hızı için tam kan viskozitesinin, derin ven trombozunun risk faktörlerinden bağımsız olduğunu gösterilmiştir (DSH, TKV=OR=5.241; %95 GA, 2.138-12.847; YSH'de P<0.001 ve TKV, OR=1.063; %95 GA, 1.063-1.102; P=0.001). **Sonuç:** Sonuç olarak, derin ven trombozu olan hastalarda tam kan viskozitesi anlamlı ve bağımsız bir risk faktörüdür.

Anahtar Kelimeler: Kan viskozitesi; venöz tromboz

Deep vein thrombosis (DVT) is defined as the presence of thrombosis in deep veins and often occurs in lower extremities. It is significantly a cause of mortality and morbidity in the long term due to post-thrombolytic events.[1-3]

The main factors for venous thrombosis are endothelial damage, changes in blood flow and hypercoagulability.[2] This is caused by changes in blood flow, blood viscosity, especially hyperviscosity, in addition, increased shear stress in hyperviscosity causes endothelial damage and thrombosis. This increase in blood viscosity is closely related to cardiovascular diseases.[4-6]

Blood viscosity measurement is difficult because there is no standard method and it needs special equipment such as a viscosimeter. However, it is possible to calculate whole blood viscosity (WBV) with a validated equation from hematocrit (HCT) and total plasma protein levels (TP) for low and high shear rate; obtaining an estimated value about WBV with this simple formula can provide clinicians a new tool for patient bedside evaluations.[7]

In this context, it was aimed to investigate the possible relationship between WBV and deep vein thrombosis.

MATERIAL AND METHODS

Patients who applied to cardiology and cardiovascular surgery outpatient clinics of Kahramanmaraş Sütçü İmam University, with complaints of foot pain and/or foot swelling between 2016 and 2018, were retrospectively screened. 116 of the 350 patients were diagnosed with DVT and 50 of them were analyzed because they had inclusion criteria for the study (Figure 1). The control group was consisted of 44 healthy subjects with foot pain and foot swelling complaints who had no deep vein thrombosis and no any acute or chronic disease. Both groups included patients of similar age and

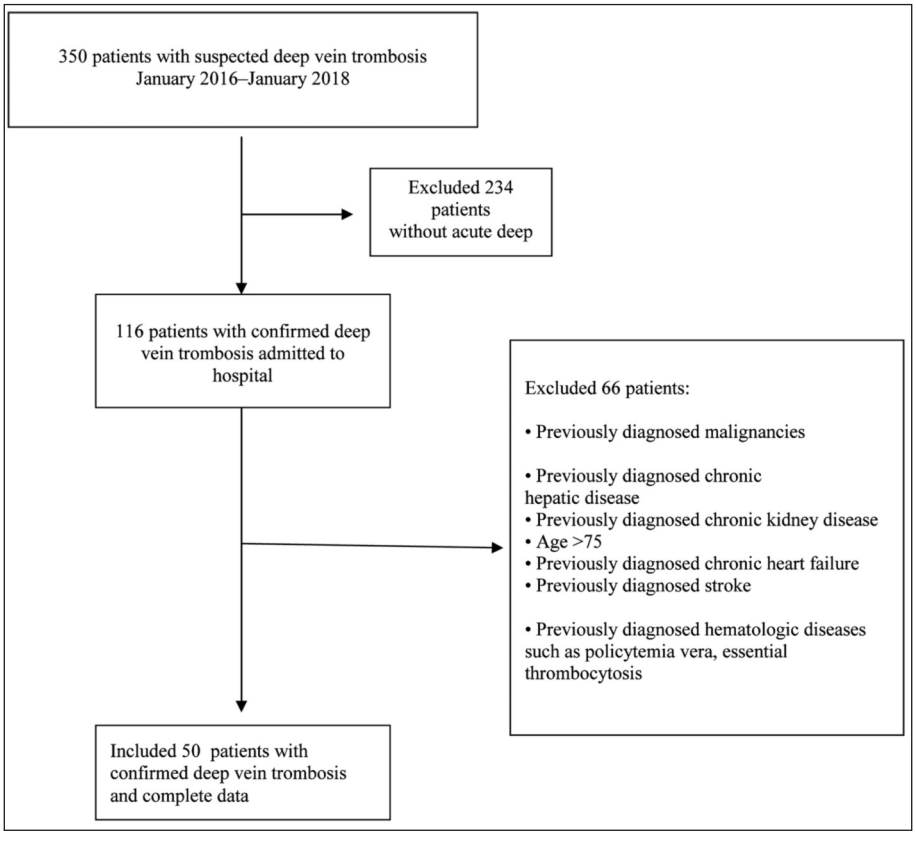

FIGURE 1: Flow chart shows the patient selection process.

gender. Physical examination findings, visualization of the material by ultrasonographic examination and treatment requirements were searched for the diagnosis of deep vein thrombosis. Patients with chronic renal failure, severe hepatic insufficiency, chronic deep vein thrombosis, hematological disorders, severe heart failure, lymphatic or venous system mediated chronic stasis, a known malignity or patients over 75 years old, bedbound due to stroke were excluded from the study. The clinical and demographic characteristics, the findings of physical examination, laboratory values, WBV values of all patients were obtained from the patient registration system and recorded, then, they were compared to the healthy group.

The estimation of WBV was executed in both high shear rate (HSR= 208/s) and low shear rate (LSR= 0.5/s) through previously validated formulas that utilize hematocrit and total plasma protein concentration.

For HSR, the WBV (208/s) formula is as follows: (0.12 × HcT) + 0.17 (TP-2.07) and for LSR, WBV (0.5/s) is: (1.89 × HcT) + 3.76 (TP-78.42), where HcT is hematocrit in %, TP is total protein concentration in g/L, and WBV is whole blood viscosity in centipoise (cP).[8-10]

STATISTICAL ANALYSIS

Data collected for the study was analyzed through SPSS program version 17 (SPSS Inc., Chicago, IL), and a two-sided p-value ≤0.05 was found out to be statistically significant. Continuous data were expressed as mean ± standard deviation or median (min-max), and categorical data as percentages. Means were compared through an independent sample t-test, and as no normal distribution was found out, the Mann-Whitney U test with median was used. Chi-square test was used to evaluate categorical data. The Spearman correlation test was used for correlation evaluation. In order to identify the optimal cutoff point of HSR and LSR for the prediction of DVT, a receiver operator characteristic (ROC) curve analysis was performed MedCalc (v12.7.8) was used to perform ROC curve analysis. In the prediction of DVT, the area under the curve (AUC) with 95% confidence interval (CI) was calculated. The optimal cutoff value of HSR and LSR were determined as the value conjoined with the highest sum of sensitivity and specificity-1. In order to quantify the association of variables with DVT, univariate analysis was used. It was found out that the variables were statistically significant in the univariate analysis and in order to determine the independent factors of DVT, other potential confounders were used in the multivariate logistic regression model with the forward stepwise method.

RESULTS

The average age of the patients included in the study was 45±12 years and the age and gender distribution in the control group were similar in the group with deep vein thrombosis. As Table 1 summarizes, the differences in hemoglobin values, platelet counts, total protein, albumin, ALT, and AST values were statistically significant between the groups. In addition, both the WBV at LSR and HSR were significantly higher in the group with deep vein thrombosis. (17.2 (14.6-19.4) vs. 16.5 (13.1-19.2), p=0.023); 61.3 (10.0-108.2 vs. 47.0 (-29.5-98.9) p=0,031, respectively). In our study, WBV at LSR and WBV at HSR were positively correlated with CRP, total protein, hemoglobin, and hematocrit (Tables 2, 3).

The optimal cutoff level of WBV at LSR levels in the prediction of DVT was >17.18, with a specificity of 70.5% and sensitivity of 54.0% (AUC= 0.636; 95% CI, 0.530–0.733; *P*=0.018) (Figure 2). Additionally, the optimal cutoff level of WBV at HSR levels in the prediction of DVT was >56.9.18, with a specificity of 62% and sensitivity of 59.1% (AUC=0.630; 95% CI, 0.524–0.727; *P*=0.025 (Figure 3).

Two different models were composed to evaluate the predictiveness of WBV parameters for each shear rate (Table 4) in the multivariate analysis. In model-1, WBV at LSR levels (OR=5.00; 95% CI, 2.037-12.269; *P*<0.001), hemoglobin (OR=8.732; 95% CI, 2.816- 27.077; *P* <0.001), number of platelets (OR=1.018; 95% CI, 1.005- 1.031; *P*=0.005) and albumin (OR=0.122; 95% CI, 0.025-0.605; *P*=0.010) were conjoined with an increased

TABLE 1: Baseline characteristics of study patients.

	All Patients (n:94)	Deep Vein Thrombosis (n:50)	Control Group (n:44)	p
Age (years)	45±12	45±14	44±10	0.835
Male/female	43/51	26/24	17/27	0.197
Hemoglobin (g/dl)	13.4 (9.8-18.2)	13.8 (9.8-18.2)	12.8 (11-14.3)	0.04
Platelets counts (10^3)	305±74	328±84	280±50	0.002
Hematocrit (%)	42.2 (32-51.8)	42.2 (32-51.8)	42.2 (32-51.7)	0.994
Total protein (g/dl)	7.1 (4.9-8.4)	7.3 (6.2-8.4)	6.9 (4.9-8.1)	0.022
Albumin (g/dl)	4.1 (2.8-5.1)	4 (2.8-5.1)	4.2 (3.2-5.1)	0.034
BUN (mg/dl)	15 (6-51)	16 (6-51)	13 (6-26)	0.392
Creatinine (mg/dl)	0.7±0.1	0.7±0.2	0.7±0.1	0.309
Sodium (mmol/l)	140±3	140±4	140±3	0.320
Potassium (mmol/L)	4.2±0.4	4.2±0.4	4.2±0.3	0.445
Chlorine (mmol/L)	104 (95-123)	103 (95-112)	105 (98-123)	0.169
ALT (U/l)	25 (8-67)	27 (9-67)	21 (8-40)	0.050
AST (U/l)	25±10	28±12	22±7	0.016
Fasting glucose (mg/dL)	107 (71-270)	110 (73-266)	102 (71-270)	0.074
CRP (mg/dl)	13.6 (2-94)	15 (3-94)	11 (2-38)	0.844
WBV at LSR	16.8 (13.1-19.4)	17.2 (14.6-19.4)	16.5 (13.1-19.2)	0.023
WBV at HSR	54.6 (-29.5-108.2)	61.3 (10.0-108.2)	47.0 (-29.5-98.9)	0.031

BUN: Blood urea nitrogen; ALT: Alanine aminotransferase; AST: Aspartat aminotransferaz; CRP: C-reactive protein; WBV: Whole blood viscosity; LSR: Low shear rate; HSR: High shear rate.

risk of DVT, after adjusting for the variables were statistically significant in the univariate analysis and for the variables correlated with the WBV at LSR level.

In the model-2, WBV at HSR levels (OR= 1.068; 95% CI, 1.028-1.110; *P*=0.001), hemoglobin (OR=7.357; 95% CI, 2.573- 21.037; *P* <0.001), number of platelets (OR=1.017; 95% CI, 1.005-1.028; *P*=0.005) and albumin (OR=0.155; 95% CI, 0.024-0.552; *P*=0.007) were also conjoined with an increased risk of DVT, after adjusting for the variables found to be statistically significant in the univariate analysis and for the variables correlated with the WBV at HSR level (Table 5).

TABLE 2: Spearman correlation coefficients for WBV at LSR levels.

	WBV at LSR	P value
CRP (mg/dl)	-0.245	0.018
Hemoglobin (g/dL)	0.417	<0.001
Hematocrit (%)	0.467	<0.001
Total protein (g/dl)	0.879	<0.001

CRP: C-reactive protein.

TABLE 3: Spearman correlation coefficients for WBV at HSR levels.

	WBV at HSR	P value
CRP (mg/dl)	-0.237	0.021
Hemoglobin (g/dL)	0.366	<0.001
Hematocrit (%)	0.378	<0.001
Total protein (gr/dl)	0.950	<0.001

CRP: C-reactive protein.

DISCUSSION

This is the first study to show that WBV both at LSR and HSR in patients with deep vein thrombosis are higher than those in the control group, at the same time, that WBV both at LSR and HSR are independent predictors of deep vein thrombosis.

The three factors described by Virchow are necessary for the initiation of the thrombosis process. These include endothelial damage, impaired blood flow, and increased blood clotting tendency. Blood flow impairment is closely related to blood viscosity, and increased blood viscosity leads to thrombosis susceptibility. Blood

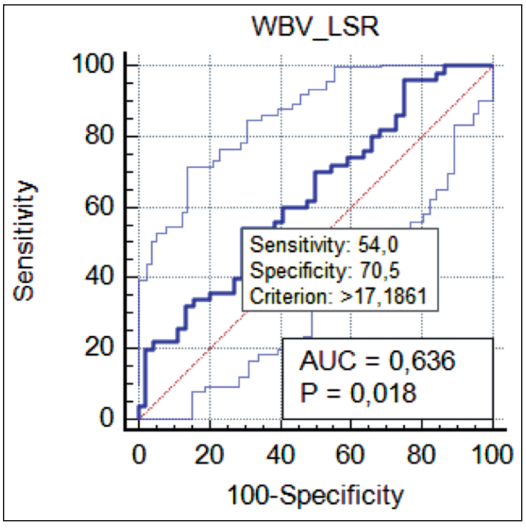

FIGURE 2: ROC curve analysis for WBV at LSR.

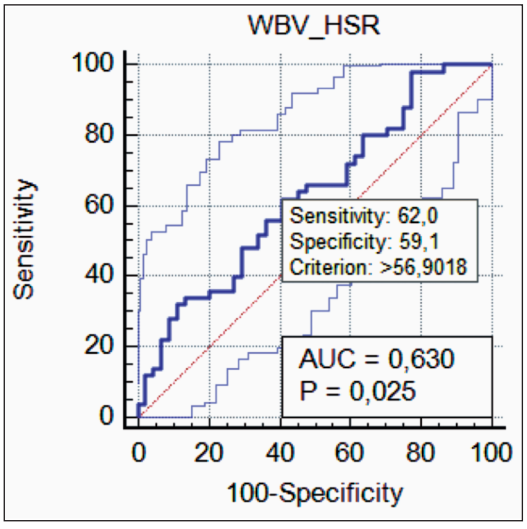

FIGURE 3: ROC curve analysis for WBV at HSR.

TABLE 4: Univariate and multivariate analyses for predicting DVT (Model 1).

	Univariate			Multivariate		
Variable	**p**	**OR**	**(95% CI)**	**p**	**OR**	**(95% CI)**
Statistically significant variables						
WBV-LSR	<0.010	1.622	1.123-2.344	<0.001	5.241	2.138-12.847
Hemoglobine	0.003	1.707	1.198-2.432	<0.001	9.644	3.104- 29.962
Platelets counts	0.003	1.010	1.003-1.017	0.003	1.017	1.006- 1.029
Albumin	0.030	0.380	0.159-0.910	0.008	0.122	0.026-0.579
ALT	0.022	1.053	1.008-1.100			
AST	0.021	1.060	1.009-1.114			
Variables which correlated with WBV-LSR						
CRP	0.122	1.029	0.993-1.066			
Hematocrit	0.988	1.001	0.912-1.098	<0.001	0.508	0.361-0.716

All the variables from Table 1 were examined and only those significant at p<0.05 level and correlated with WBV-LSR are shown in univarite analysis. Multivariate logistic regression analysis including all the variables in univariate analysis with enter method. Bun: Blood urea nitrogen; ALT: Alanine aminotransferase; AST: Aspartat aminotransferaz; CRP: C-reactive protein; WBV: Whole blood viscosity; LSR: Low shear rate; HSR: High shear rate; CI: Confidence interval; OR: Hazard ratio.

TABLE 5: Univariate and multivariate analyses for predicting DVT (Model 2).

	Univariate			Multivariate		
Variable	**p**	**OR**	**(95% CI)**	**p**	**OR**	**(95% CI)**
Statistically significant variables						
WBV-HSR	<0.010	1.622	1.123-2.344	0.001	1.063	1.026-1.102
Hemoglobin	0.003	1.707	1.198-2.432	<0.001	6.601	2.336- 16.530
PLT	0.003	1.010	1.003-1.017	0.004	1.016	1.005- 1.026
Albumin	0.030	0.380	0.159-0.910	0.003	0.097	0.021-0.445
ALT	0.022	1.053	1.008-1.100			
AST	0.021	1.060	1.009-1.114			
Variables which correlated with WBV-HSR						
CRP	0.122	1.029	0.993-1.066			
Hematocrit	0.988	1.001	0.912-1.098	<0.001	0.573	0.432-0.759

All the variables from Table 1 were examined and only those significant at p<0.05 level and correlated with WBV-LSR are shown in univarite analysis. Multivariate logistic regression analysis including all the variables in univariate analysis with enter method. Bun: Blood urea nitrogen; ALT: Alanine aminotransferase; AST: Aspartat aminotransferaz; CRP: C-reactive protein; WBV: Whole blood viscosity; LSR: Low shear rate; HSR: High shear rate; CI: Confidence interval; OR: Hazard ratio.

viscosity is increased by low blood flow and erythrocyte aggregation. Increased blood viscosity becomes effective by ensuring that thrombocyte aggregates are blocked in small vessels.[11] Blood viscosity was investigated both in arterial thrombus formation and venous embolism formation. Gündoğan et al., found that patients who suffered from acute myocardial infarction had significantly higher blood viscosity than the control group.[12] Studies in patients with retinal vein thrombosis also revealed that blood viscosity correlates with retinal venous thrombosis.[13,14] In the present study, as expected, increased viscosities had close relationship with deep vein thrombosis, similar to other studies in the literature. However, in our study, the viscosity was calculated not by the viscometer but by the hematocrit and total protein values. This may be a restriction, but plasma viscosity is known to show a positive correlation with hematocrit, red blood cell, plasma proteins, CRP, cholesterol, triglycerides, uric acid, von Willebrand factor.[15-17] In the present study, WBV both at LSR and HSR was found to be correlated with hematocrit, total protein, and CRP, in accordance with the literature. This makes it possible to consider that the obtained values can be trusted.

Increased plasma viscosities are closely associated with shear stress. Duyguluel et al., found that serum viscosities in aorta were an independent predictor, which was explained by increased shear stress.[9] Similarly, Çetin et al. found that serum viscosity was an independent predictor in predicting mitral annular calcification.[18] Increased shear stress creates endothelial damage and inflammation. Endothelial damage is one of the prerequisites for thrombosis. From here, the increase in viscosity can indirectly cause endothelial damage and increase the tendency to thrombosis. In the present study, the correlation between CRP and viscosity and the increase of viscosity in patients with deep vein thrombosis support the fact that the increased viscosity can lead to the endothelial damage.

Another factor for thrombosis is platelet count. The increase in platelet counts will cause an increase in serum viscosities and will result in thrombus formation. In the present study, the platelet count in patients with deep vein thrombosis was found out to be higher than in control group, and platelet count was an independent predictor for deep vein thrombosis. Similarly, hemoglobin levels were higher in patients with deep vein thrombosis than in control group, and hemoglobin was an independent predictor of deep vein thrombosis. This finding suggested that increased hemoglobin contributes to deep vein thrombosis by increasing blood viscosity.

In conclusion, WBV was demonstrated as a neglected and underestimated predictor of deep vein thrombosis. The increase in viscosity increases the tendency to thrombosis by causing endothelial damage as a result of both the deterioration of blood flow and shear stress. Blood viscosity could play an important role in the management of the diseases as well as predicting them if it could be proven by clinical studies.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Hakan Güneş, Mehmet Kirişci;* ***Design:*** *Hakan Güneş, Mehmet Kirişci;* ***Control/Supervision:*** *Hakan Güneş, Mehmet Kirişci;* ***Data Collection and/or Processing:*** *Hakan Güneş, Mehmet Kirişci;* ***Analysis and/or Interpretation:*** *Hakan Güneş;* ***Literature Review:*** *Hakan Güneş, Mehmet Kirişci;* ***Writing the Article:*** *Hakan Güneş;* ***Critical Review:*** *Hakan Güneş, Mehmet Kirişci*

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